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Multiple squamous cell carcinomas in a psoriatic patient following high-dose photochemotherapy and cyclosporin treatment: response to long-term acitretin maintenance

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Summary

Cumulative toxicity is a well known limitation of antipsoriatic treatments. In particular, the induction of multiple squamous cell carcinomas following long-term PUVA treatment is well established. In the present report, a psoriatic patient is described who was treated for more than 14 years with photochemotherapy (PUVA) and who received excessive amounts of topical corticosteroids. The patient developed, in total, 34 squamous cell carcinomas. In all, three squamous cell carcinomas developed during long-term PUVA treatment, and 21 carcinomas appeared during 16 months of treatment with cyclosporin. Subsequently, a marked inhibition of the occurrence of new tumours occurred during prolonged treatment with acitretin, and no new tumours have appeared during the last 4 years of continuous treatment with this retinoid at a dose of 60 mg/day.

Modulation of the expression of PUVA-induced squamous cell carcinomas by cyclosporin and acitretin are discussed. The present report lends support to the hypothesis that cyclosporin causes an increased occurrence of PUVA-induced carcinomas, whereas acitretin (60 mg/day) is of value in preventing the occurrence of new squamous cell carcinomas in patients who were treated with long-term PUVA.

Several studies have demonstrated that prolonged photochemotherapy (PUVA) is associated with an increased occurrence of squamous cell carcinomas.^{1–4} Deaths due to metastasizing squamous cell carcinomas due to excessive PUVA treatment have occurred.⁵ Cyclosporin treatment also has been reported to be associated with an increased occurrence of squamous cell carcinomas.^{6–7} In particular, the combination of both treatments may increase the cancer risk substantially.^{8,9}

Systemic treatment with 13-*cis*-retinoic acid, etretinate and acitretin have reduced the occurrence of non-melanoma skin cancers in cancer-prone conditions such as the basal cell naevus syndrome, xeroderma pigmentosum, renal transplantation and sun-damaged skin.¹⁰

In this report, a patient is described who was treated for 14 years with photochemotherapy, resulting in three squamous cell carcinomas. During 16 months treatment with cyclosporin, 21 squamous cell carcinomas appeared.¹¹ Subsequently, treatment with acitretin (60 mg/day) for 6 years, resulted in a decreased occurrence of new tumours (in the first 2 years) and the absence of new carcinomas (over the last 4 years). The

modulation of the occurrence of PUVA-induced carcinomas by cyclosporin and acitretin is discussed.

Case report

A 59-year-old man suffered from extensive recalcitrant psoriasis for more than 40 years. At times the psoriatic lesions became erythrodermic. The patient had been treated with dithranol, methotrexate and topical corticosteroids during the first 20 years. There was no history of radiotherapy treatment nor of arsenic ingestion. From 1975 onwards, the patient was treated with more than 2500 PUVA exposures, in total. The treatment schedule was four times per week, without intermissions, up to 1989. During these 14 years of intensive PUVA treatment, the patient was treated simultaneously with potent topical corticosteroids. Each week, the patient used 125 g/week of deoxymethasone (2.5 mg/g) ointment, for many years. PUVA treatment was discontinued at the time the patient developed numerous lentigines and three squamous cell carcinomas. Etretinate, in combination with topical corticosteroids, and methotrexate, in combination with topical corticosteroids, were ineffective.

Cyclosporin A was started at a dose of 10 mg/kg per day. At that time, no squamous cell carcinomas were present. However, numerous lentigines and multiple striae were observed. The severe extent of the psoriatic lesions necessitated systemic treatment. At first, this treatment proved to be effective. However, a severe relapse occurred at a dose of 5 mg/kg per day. After initiation of cyclosporin treatment, new squamous cell carcinomas continued to appear. During 16 months of treatment with cyclosporin, 21 squamous cell carcinomas had appeared (one on the lower lip, three on the arms and 17 on the legs).¹¹ In this stage, the patient was referred to our centre for further treatment.

The patient was admitted for 7 months. Severe erythroderma was present. The hair was sparse, and extensive psoriatic nail changes were observed. At the flexures, multiple striae were observed. On the legs and presternal areas, multiple hyperkeratotic papules were present. A thoracic kyphosis was evident. Both eyes showed cataracts. Blood investigations revealed a cortisone level of 0.07 $\mu\text{mol/l}$ (normal range 0.19–0.55 $\mu\text{mol/l}$). X-ray examination of the vertebral column revealed severe osteoporotic changes with block vertebra at C6 and C7, and compression of several thoracic vertebra.

Treatment with cyclosporin and topical corticosteroids was discontinued. At the erythrodermic stage, acitretin, 25 mg/day, was instituted, and topical treatments consisted of crude coal tar (3–5% in zinc paste or petrolatum-lanette), chrysarobin ointment (up to 3%), short-contact dithranol (0.05–1%) and 24 h applications of dithranol in lanette cream and Optiderm ointment (Hermal, Hamburg, Germany). After 3 months of treatment as an in-patient, the lesions had improved considerably, and a better inspection of the hyperkeratotic lesions was possible. In this stage, the dose of acitretin was increased to 50 mg/day.

Following resolution of the psoriatic lesions, examination of the skin revealed numerous lentigines and circumscribed hyperkeratoses predominantly on the legs, presternal area and arms (Fig. 1). Some of these lesions were hyperkeratotic and others were ulcerated (Fig. 2). The histopathological appearance was of well-differentiated squamous cell carcinomas (Fig. 3). Up to January 1992, 13 squamous cell carcinomas and four PUVA keratoses were excised from the legs, and four keratoses were removed from the trunk and arms. Areas with multiple and small sized hyperkeratotic lesions were treated with 5-fluorouracil cream.

After 7 months of treatment, the extent and severity of the psoriatic lesions was limited, and treatment was

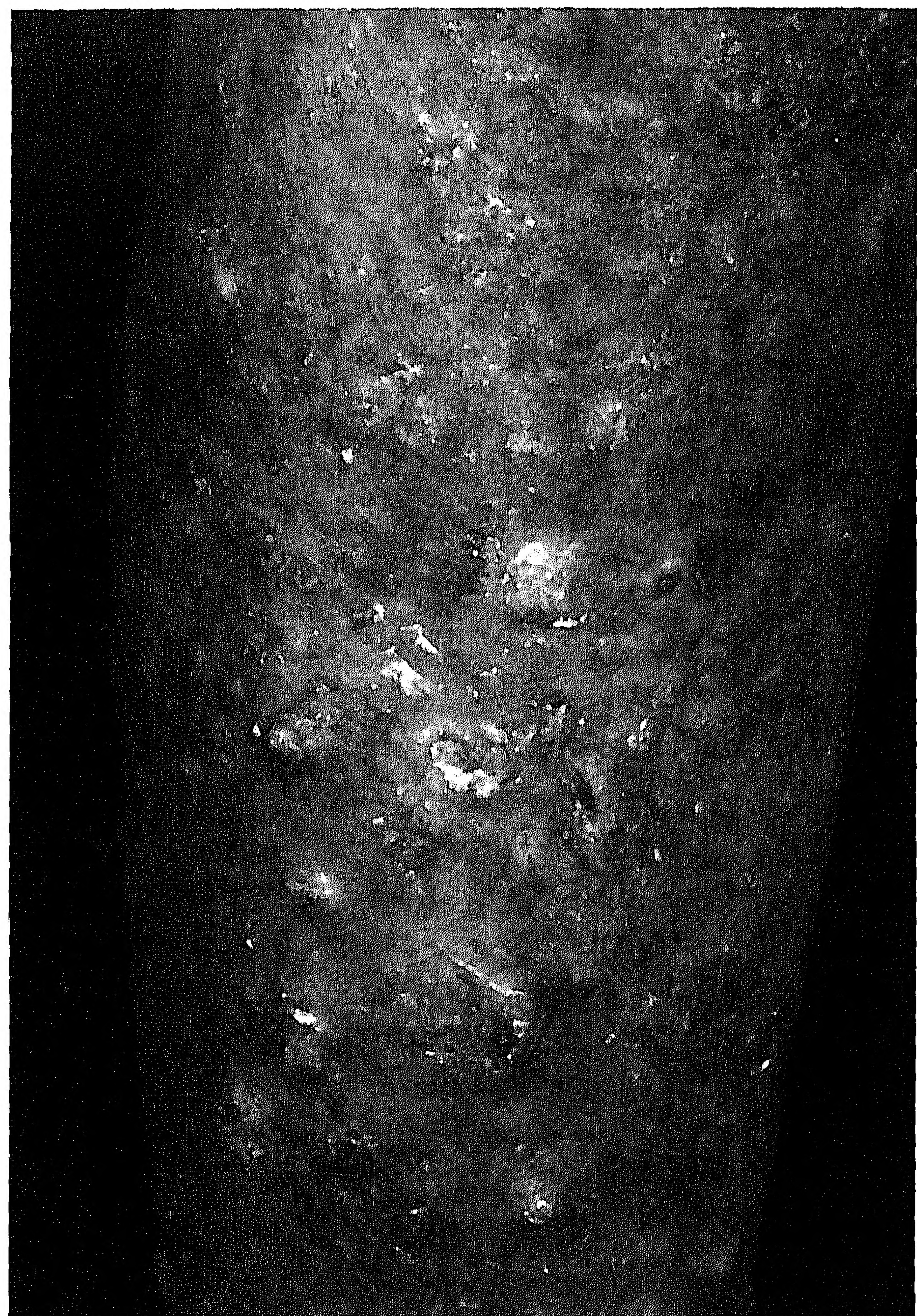


Figure 1. Multiple PUVA keratoses and squamous cell carcinomas on the thigh.

continued as an out-patient. From September 1990 onwards, the dose of acitretin was between 50 and 70 mg/day. From January 1992 to the present (June 1996) no new PUVA keratoses or squamous cell carcinomas have appeared. During these years, the severity of the psoriatic lesions was limited to some plaques, which could be managed with topical treatments such as calcipotriol ointment and tar preparations.

Two months after discontinuation of topical corticosteroids and cyclosporin, the serum cortisol was 0.28 $\mu\text{mol/l}$. In order to compensate for the adrenal gland insufficiency, cortisone acetate, 37.5 mg/day, was administered. During the subsequent 18 months, the level of endogenous cortisol reverted to normal (0.30 $\mu\text{mol/l}$) and the level of adrenocorticotrophic hormone also was normal (4.7 pmol/l). In 1990, extracapsular cataract extraction and lens implantation were performed. An X-ray examination and skeletal densitometry revealed severe signs of osteoporosis. For this

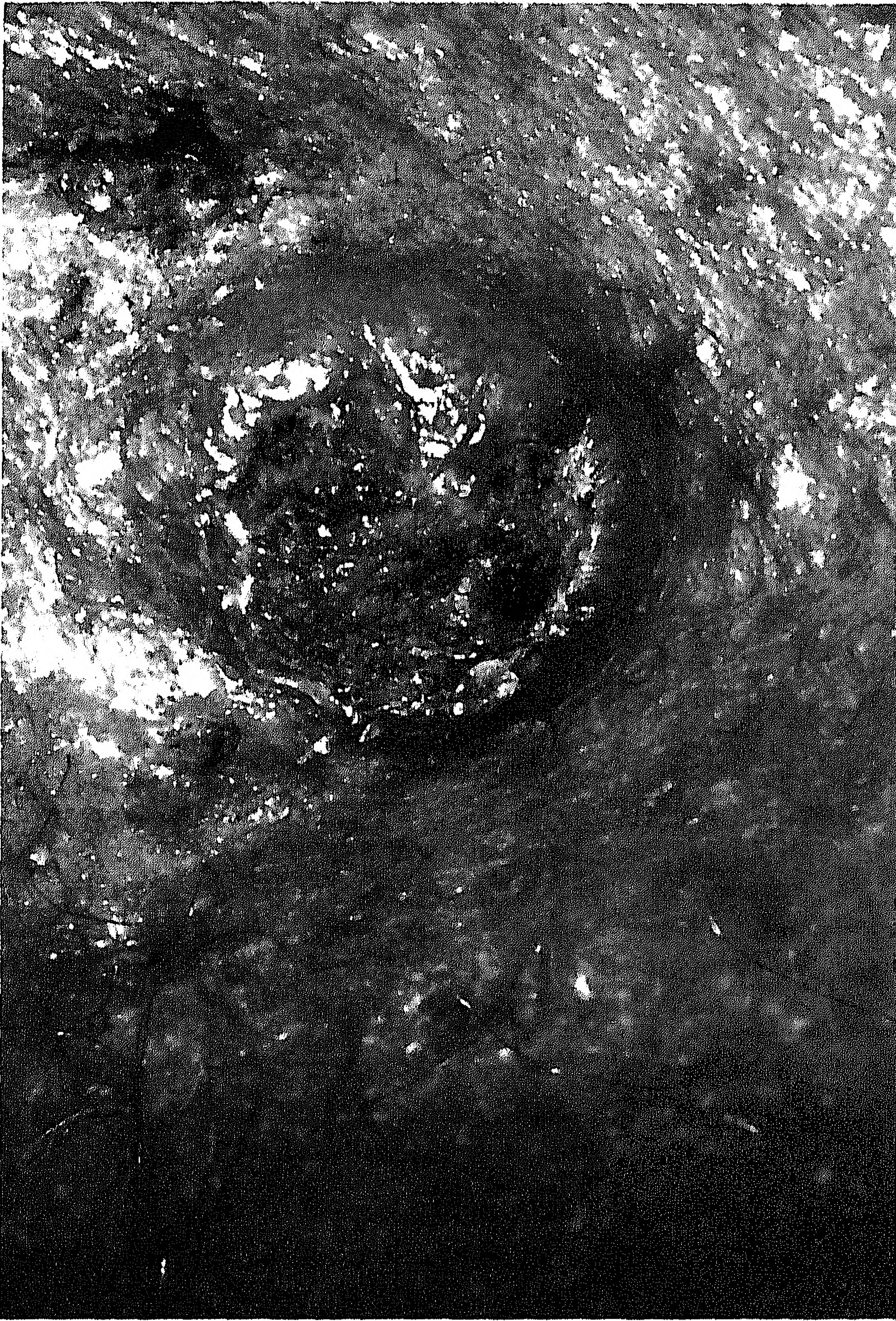


Figure 2. An ulcerating PUVA keratosis on the lower leg.

reason the patient was treated with sodium fluoride (25 mg 3 times daily), 1,25-dihydroxyvitamin D₃ (0.1 mg on alternate days), calcium Sandoz (1000 mg a day) and aminohydroxypropylidene diphosphonate (50 mg three times a day). In November 1992, X-ray examination and ossal densometry were normal. Therefore, treatment for osteoporosis was discontinued. It is highly likely that the osteoporosis and the development of cataract were due to the excessive use of topical corticosteroids.

Discussion

Long-term PUVA therapy is a well established cause of multiple squamous cell carcinomas. The spontaneous course of PUVA-induced malignancies has not been documented, to the best of our knowledge. It is, however, the principle of ultraviolet (UV) induced carcinogenesis that the damage is permanent, and that repeated UV exposures exert their biological effect according to a cumulative dose-response relationship.¹⁻⁴ Cyclosporin, as an immunosuppressive drug, decreases the immune surveillance of the skin and, hence, results in an increased occurrence of squamous cell carcinoma.¹² In particular, during the treatment of psoriatic plaques with PUVA and cyclosporin, multiple squamous cell carcinomas have been reported.⁹⁻¹¹

In the present case, squamous cell carcinomas appeared during long-term PUVA treatment and continued to appear during cyclosporin treatment in high numbers. During long-term acitretin treatment, the appearance of new squamous cell carcinomas decreased



Figure 3. The histopathological appearance of a squamous cell carcinoma from the lower leg ($\times 75$).

and, eventually, for a 4-year period, no new squamous cell carcinomas have been observed. Although it cannot be excluded with certainty that the appearance of new squamous cell carcinomas during cyclosporin treatment resulted exclusively from PUVA therapy, the high frequency of tumours during cyclosporin therapy suggests that cyclosporin, following PUVA treatment, contributed to the induction of these carcinomas. It is a remote possibility that the cessation in the appearance of new squamous cell carcinomas is the result of a recovery in our patient's immune status following the discontinuation of cyclosporin. On the other hand, a direct effect of acitretin on the development of squamous cell carcinoma is more likely.

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